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L2: Entry 3 of 7 File: USPT Oct 30, 2001

US-PAT-NO: 6309633
DOCUMENT-IDENTIFIER: US 6309633 B1

TITLE: Amphiphilic drug-oligomer conjugates with hydroyzable lipophile components and methods for making and using the same

DATE-ISSUED: October 30, 2001

INVENTOR-INFORMATION:

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DATE FILED: June 19, 1999

INT-CL: [07] A61 K 9/107, A61 K 38/17, A61 K 38/28, A61 K 39/385, C07 K 1/113

US-CL-ISSUED: 424/85.1; 424/85.2, 424/85.4, 424/94.3, 424/193.1, 424/194.1, 435/188, 514/2, 514/3, 514/8, 514/12, 514/21, 514/476, 514/506, 514/579, 514/613, 514/715, 530/303, 530/345, 530/405, 530/406, 530/409, 530/410 , 530/411
US-CL-CURRENT: 424/85.1; 424/193.1, 424/194.1, 424/85.2, 424/85.4, 424/94.3, 435/188, 514/12, 514/2, 514/21, 514/3, 514/476, 514/506, 514/579, 514/613, 514/715, 514/8, 530/303, 530/345, 530/405, 530/406, 530/409, 530/410 , 530/411

FIELD-OF-SEARCH: 424/85.1, 424/85.2, 424/85.4, 424/85.5, 424/85.6, 424/85.7, 424/94.3, 424/178.1, 424/179.1, 424/193.1, 424/194.1, 435/188, 514/2, 514/3, 514/8, 514/12, 514/21, 514/476, 514/506, 514/579, 514/613, 514/715, 530/300, 530/303, 530/322, 530/345, 530/350, 530/351, 530/403, 530/405, 530/406, 530/409, 530/410, 530/411

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ART-UNIT: 163

PRIMARY-EXAMINER: Russel; Jeffrey E.

ATTY-AGENT-FIRM: Myers Bigel Sibley & Sajovec, P.A.

ABSTRACT:

The invention provides a drug-oligomer conjugate having the following general formula: ##STR1##

wherein D is a therapeutic drug moiety; H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars; L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-26 carbon atoms, cholesterol, adamantane and fatty acids; o is a number from 1 to the maximum number of covalent bonding sites on H; m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L and --H--L substituents; the H--L bond(s) are hydrolyzable and the D--L' bond(s), when

present, are hydrolyzable; the conjugate being further characterized by one of the following: (i) m is 0 and p is at least 1; (ii) n is 0 and p is at least 1; (iii) m and n are each 0 and p is at least 1; (iv) p is 0 and m and n are each at least 1. The therapeutic drug moiety is preferably a therapeutic protein or peptide, preferably insulin or a functional equivalent thereof.

60 Claims, 3 Drawing figures

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L2: Entry 3 of 7 File: USPT Oct 30, 2001

DOCUMENT-IDENTIFIER: US 6309633 B1
TITLE: Amphiphilic drug-oligomer conjugates with hydroyzable lipophile components and methods for making and using the same

CLAIMS:

1. A drug-oligomer conjugate having the following general formula:

D--[(H--S.sub.n)--L.sub.o].sub.p (Formula 11)

wherein

D is a therapeutic drug moiety;

H is a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

n is a number from 1 to the maximum number of covalent bonding sites at which S can form a bond with H;

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with S;

p is a number from 1 to the maximum number of covalent bonding sites at which --[(H--Sn)--Lo] can form a bond with D; and

the S--H bond is hydrolyzable.

5. A drug-oligomer conjugate having the following general formula:

D--[(H--S.sub.n --H'.sub.q)--L.sub.o].sub.p (Formula 12)

wherein

D is a therapeutic drug moiety;

H and H' are hydrophilic moieties, individually selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

n is a number from 1 to the maximum number of covalent bonding sites at which S can form a bond with H;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can form a bond with S;

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with S;

p is a number from 1 to the maximum number of covalent bonding sites at which --[(H--S.sub.n --H'.sub.q)--L.sub.o] can form a bond with D; and

the H--S bond is hydrolyzable.

9. The drug-oligomer conjugate of claim 5 wherein the H'--L bond is non-hydrolyzable, and wherein the (H--S.sub.n --H'.sub.q)--L.sub.o oligomer comprises an H'--L subunit selected from the group consisting of:

CH.sub.3 (CH.sub.2).sub.n (OC.sub.2 H.sub.4).sub.m OH (Formula 3)

wherein n=3 to 25 and m=1 to 7;

CH.sub.3 (CH.sub.2).sub.n (OC.sub.2 H.sub.4).sub.m OCH.sub.2 CO.sub.2 H (Formula 4)

wherein n=3 to 25 and m=1 to 6;

R--(OC.sub.2 H.sub.4).sub.m CH.sub.2 CO.sub.2 H (Formula 6)

wherein m=0 to 5 and R=cholesterol or adamantane;

CH.sub.3 (CH.sub.2 --CH.dbd.CH).sub.6 (CH.sub.2).sub.2 (OC.sub.2 H.sub.4).sub.m OH (Formula 8)

wherein m=1 to 7; and

CH.sub.3 (CH.sub.2 --CH.dbd.CH).sub.6 (CH.sub.2).sub.2 CX(OC.sub.2 H.sub.4).sub.m OH (Formula 9)

wherein m=1 to 7 and X=NH.

11. A drug-oligomer conjugate having the following general formula:

D--[(H--H'.sub.q --S.sub.n)--L.sub.o].sub.p (Formula 13)

wherein

D is a therapeutic drug moiety;

H and H' are hydrophilic moieties, individually selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids;

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can form a bond with H;

n is a number from 1 to the maximum number of covalent bonding sites at which S can form a bond with H';

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with S;

p is a number from 1 to the maximum number of covalent bonding sites at which --[(H--H'.sub.q --S.sub.n)--L.sub.o] can form a bond with D; and

the H--S bond is hydrolyzable.

15. A drug-oligomer conjugate having the following general formula:

D--[(H--H'.sub.q)--L.sub.o].sub.p (Formula 10)

wherein

D is a therapeutic drug moiety;

H and H' are hydrophilic moieties, individually selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids;

the H--H' bond is hydrolyzable and the H'--L bond is not hydrolyzable;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can form a bond with H;

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with H'; and

p is a number from 1 to the maximum number of covalent bonding sites at which --[(H--H'.sub.q)--L.sub.o] can form a bond with D.

21. A drug-oligomer conjugate having the following general formula: ##STR14##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-26 carbon atoms, cholesterol, adamantane and fatty acids;

o is a number from 1 to the maximum number of covalent bonding sites on H; and

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1.

26. A drug-oligomer conjugate having the following general formula: ##STR15##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids:

o is a number from 1 to the maximum number of covalent bonding sites on H;

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1; and

wherein the D--H and D--H' bonds, when present, are independently selected from the group consisting of carbamate, amide and secondary amine.

28. A drug-oligomer conjugate having the following general formula: ##STR16##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

o is a number from 1 to the maximum number of covalent bonding sites on H;

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1; and

wherein the H--L bond is selected from the group consisting of ester and carbonate.

32. A drug-oligomer conjugate having the following general formula: ##STR17##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

o is a number from 1 to the maximum number of covalent bonding sites on H;

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1; and

wherein the therapeutic drug moiety has at least one available moiety for conjugation selected from the group consisting of --NH2; --OH and --SH, and wherein at least one of the available moieties is conjugated to the H--L moiety.

35. The drug-oligomer conjugate of claim 32 wherein D is an antigen from an organism or associated with a disease state, selected from the group consisting of adenoviruses; anthrax; Bordetella pertussus; Botulism; bovine rhinotracheitis; Branhamella catarrhalis; canine hepatitis; canine distemper; Chlamydiae; Cholera; coccidiomycosis; cowpox; cytomegalovirus; Dengue fever; dengue toxoplasmosis; Diphtheria; encephalitis; Enterotoxigenic E. coli; Epstein Barr virus; equine encephalitis; equine infectious anemia; equine influenza; equine pneumonia; equine rhinovirus; Escherichia coli; feline leukemia; flavivirus; Globulin; haemophilus influenza type b; Haemophilus influenzae; Haemophilus pertussis; Helicobacter pylon; Hemophilus; hepatitis; hepatitis A; hepatitis B; Hepatitis C; herpes viruses; HIV; HIV- 1 viruses; HIV-2 viruses; HTLV; Influenza; Japanese encephalitis; Klebsiellae species; Legionella pneumophila; leishmania; leprosy; lyme disease; malaria immunogen; measles; meningitis; meningococcal; Meningococcal Polysaccharide Group A; Meningococcal Polysaccharide Group C; mumps; Mumps Virus; mycobacteria; Mycobacterium tuberculosis; Neisseria; Neisseria gonorrhoeae; Neisseria meningitidis; ovine blue tongue; ovine encephalitis; papilloma; parainfluenza; paramyxoviruses; Pertussis; Plague; Pneumococcus; Pneumocystis carinii; Pneumonia; Poliovirus; Proteus species; Pseudomonas aeruginosa; rabies; respiratory syncytial virus; rotavirus; Rubella; Salmonellae; schistosomiasis; Shigellae; simian immunodeficiency virus; Smallpox; Staphylococcus aureus; Staphylococcus species; Streptococcus pneumoniae; Streptococcus pyogenes; Streptococcus species; swine influenza; tetanus; Treponema pallidum; Typhoid; Vaccinia; varicella-zoster virus; and Vibrio cholerae.

38. A drug-oligomer conjugate having the following general formula: ##STR18##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids having 4-26 carbon atoms;

o is a number from 1 to the maximum number of covalent bonding sites on H; and

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1.

40. A drug-oligomer conjugate having the following general formula: ##STR19##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

o is a number from 1 to the maximum number of covalent bonding sites on H;

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1; and

wherein H--L is selected from the group consisting of:

CH.sub.3 (CH.sub.2).sub.n CX(OC.sub.2 H.sub.4).sub.m OH (Formula 5)

wherein n=3 to 25, m=1 and X.dbd.O;

R--OCO(C.sub.2 H.sub.4 O).sub.m CH.sub.2 CO.sub.2 H (Formula 7)

wherein m=0 to 5 and R=cholesterol or adamantane; and

CH.sub.3 (CH.sub.2 --CH.dbd.CH).sub.6 (CH.sub.2).sub.2 CX(OC.sub.2 H.sub.4).sub.m OH (Formula 9)

wherein m=1 to 7 and X=O.

45. A method for solubilizing a drug in an oil containing pharmaceutical formulation comprising:

a) providing a drug-oligomer conjugate having a formula: ##STR20##

where

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

the H--L bond(s) are hydrolyzable and the D--L' bond(s), when present, are hydrolysable;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids;

o is a number from 1 to the maximum number of covalent bonding sites on H,

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1;

b) bringing the drug-oligomer conjugate of a) into association with an oil containing pharmaceutical formulation.

49. A method for providing a drug-hydrophile conjugate to a situs of a subject, the method comprising administering to the subject a drug-oligomer conjugate having the formula: ##STR21##

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, adamantane and fatty acids,

o is a number from 1 to the maximum number of covalent bonding sites on H;

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the --H', --L' and --H--L substituents, and wherein m and n are each at least 1; and

the H--L bond(s) and/or the D--L' bonds are hydrolyzable in the subject to provide the drug-hydrophile conjugate.

56. A method for providing a drug-PEG conjugate to a situs of a subject, wherein the drug component of the drug-PEG conjugate is selected from the group consisting of insulin and functional equivalents of insulin, and wherein the drug-PEG conjugate has enhanced activity in comparison with a corresponding unconjugated insulin molecule, the method comprising administering to the subject a drug-PEG-lipophile conjugate having a formula:

D--[(H--H'.sub.q)--L.sub.o].sub.p (Formula 10)

wherein

D is selected from the group consisting of insulin and functional equivalents of insulin;

H is a straight or branched PEG polymer having from 2 to 7 PEG subunits;

H' is a straight or branched PEG polymer having from 0 to 130 PEG subunits;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can form a bond with H;

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with H';

p is a number from 1 to the maximum number of covalent bonding sites at which --[(H--H'.sub.q)--L.sub.o] can form a bond with D; and

the H--H' bond is hydrolyzed in the subject to provide the drug-PEG conjugate.

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L2: Entry 4 of 7 File: USPT Oct 23, 2001

US-PAT-NO: 6306838
DOCUMENT-IDENTIFIER: US 6306838 B1

TITLE: Targeted vesicular constructs for cyto protection and treatment of h. pylori

DATE-ISSUED: October 23, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Singh; Amarjit	New Delhi			IN
Jain; Rajesh	New Delhi			IN

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Panacea Biotec Limited	New Delhi			IN	03

APPL-NO: 09/ 490127 [PALM]
DATE FILED: January 24, 2000

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
IN	141/DEL/99	January 25, 1999

INT-CL: [07] A61 K 31/685, A61 K 31/65, A61 K 31/56

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US-CL-CURRENT: 514/78; 514/152, 514/182

FIELD-OF-SEARCH: 514/78, 514/182, 514/152

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5286492	February 1994	Dettmar et al.	424/458

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WO 95/28943	November 1995	WO	
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ART-UNIT: 164

PRIMARY-EXAMINER: Weddington; Kevin E.

ATTY-AGENT-FIRM: Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

ABSTRACT:

A Novel Composition for targeted vesicular for treatment of H-Pylori infections and for protection of the cell is disclosed. The Composition Comprises Lectins, Phospholipids sterols an one or more drugs. The Composition is useful since not only it treats H-Pylori infections and other diseases associated therewith but also helps in protection of the cell walls.

12 Claims, 3 Drawing figures

WEST Search History

DATE: Monday, August 25, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=AND		
L1	(cholesterol or dipalmitoyl$ or di-palmitoyl$ or dimyristoyl$ or di-myristoyl$).clm.	3594	L1
L2	L1 and (pylori or pyloris or pyloridis or pylor or pylon or helicobacer or helicobacter or helliobacter or hpylori).clm.	7	L2
L3	lipid.clm. and (pylori or pyloris or pyloridis or pylor or pylon or helicobacer or helicobacter or helliobacter or hpylori).clm. not l2	12	L3
L4	L3 and lewis.clm.	0	L4
L5	t-helper.clm.	34	L5
L6	th1.clm. or th-1.clm.	140	L6
L7	L6 or l5	174	L7
L8	l7 and (pylori or pyloris or pyloridis or pylor or pylon or helicobacer or helicobacter or helliobacter or hpylori).clm. not l2 not l3	0	L8
L9	l7 and (pylori or pyloris or pyloridis or pylor or pylon or helicobacer or helicobacter or helliobacter or hpylori).clm.	0	L9
L10	l7 and (pylori or pyloris or pyloridis or pylor or pylon or helicobacer or helicobacter or helliobacter or hpylori)	2	L10

END OF SEARCH HISTORY

WEST Search History

updated 8/2003 VSP

DATE: Monday, August 25, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=AND		
L1	dc-chol or d-c-chol or dcchol	218	L1
L2	L1 and (helicobacter or pylori or pyloris or pyloridis or pylorum or hpylori or heliobacter or pylor or pylon or helicobacter)	3	L2
L3	DOTAP or DOTMA or DC-Chol	1183	L3
L4	L3 and (helicobacter or pylori or pyloris or pyloridis or pylorum or hpylori or heliobacter or pylor or pylon or helicobacter)	32	L4
L5	L4 not l2	29	L5
L6	protein near5 (kinasec or kinase-c or (kinase near c))	3755	L6
L7	l6 and (helicobacter or pylori or pyloris or pyloridis or pylorum or hpylori or heliobacter or pylor or pylon or helicobacter)	33	L7

END OF SEARCH HISTORY